

Effect of Myocardial Hypertrophy on Systolic and Diastolic Function in Children: Insights From the Force-Frequency and Relaxation-Frequency Relationships

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Objective. The objective of this study was to evaluate the effect of myocardial hypertrophy on systolic and diastolic properties of the left ventricle in children.

Background. In children with myocardial hypertrophy, ejection phase indices are invariably increased. However, indices of force-generation, e.g., end-systolic elastance and invasive indices of diastolic properties, have been studied infrequently in children with myocardial hypertrophy.

Methods. We studied 10 children with congenital aortic stenosis or coarctation of aorta and nine control patients. Systolic properties were assessed from shortening fraction, end-systolic fiber elastance (E_{es}) measured at resting heart rates, and force-frequency relationship measured at heart rates increasing from 110 to 160 beats per minute. Diastolic properties were assessed from time constant of relaxation (τ) at matched heart rates, chamber stiffness constant, myocardial stiffness constant, and relaxation-frequency relationship measured at gradually increasing heart rates.

Results. E_{es} remained unchanged by myocardial hypertrophy, however, τ was prolonged (τ_L : 27.3 ± 2.3 vs. 21.8 ± 2.2 ms, $p < 0.001$; and τ_D : 43.2 ± 3.1 vs. 34.3 ± 3.3 ms, $p < 0.001$). Both chamber and myocardial stiffness constants remained unchanged. Incremental increases in heart rate produced incremental improvement in both contraction and relaxation. Slopes of force-frequency and relaxation-frequency relationships remained unchanged in the experimental group. However, the relaxation-frequency relationship manifested a parallel shift upward.

Conclusions. In conscious, sedated children with myocardial hypertrophy, systolic function assessed by an index of force generation remains unchanged. However, relaxation is prolonged but passive diastolic properties remain unaffected. The combined effect of hypertrophy and heart rate does not alter the force-frequency and relaxation-frequency relationships.

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In both adults and children chronic pressure overload results in myocardial hypertrophy. However, the role of pressure overload hypertrophy on myocardial systolic function has remained controversial. Studies performed in adult humans and animals with pressure overload have shown left ventricular (LV) systolic function to be normal (1-3), depressed (4), or increased (5,6). Such disparity in results may be the outcome of species difference, the severity of hypertrophy, the timing of the experiments, and the techniques used, i.e., isolated heart preparations versus preparations with intact circulations.

Compared with adults, studies in children and immature animals with pressure overload hypertrophy are much less frequent. In children with myocardial hypertrophy resulting

from pressure overload, the left ventricular systolic function was increased when assessed by ejection phase indices, e.g., ejection fraction and velocity of circumferential fiber shortening (Vcf) (7,8), but the function was normal when the ejection phase indices of LV function were corrected for afterload (9). It is speculated that indices of force generation, e.g., end-systolic elastance (E_{es}) and velocity-dependent indices of contractility, e.g., Vcf, represent different mechanistic aspects of the contractile process. Therefore, a change in one may not be associated with a concomitant change in the other. Although described in detail in adults, E_{es} has rarely been studied in children with pressure overload hypertrophy.

In adults, diastolic properties of the hypertrophied myocardium exposed to chronic pressure overload have been studied extensively. Based on these studies, the time constant of relaxation and myocardial stiffness constant have been used as gold standards for assessing diastolic properties of the hypertrophied myocardium. In children, diastolic properties of the hypertrophied left ventricle have been assessed in congenital aortic stenosis (10) and in children with systemic hypertension (11), using noninvasive indices of left ventricular filling. These

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Abbreviations and Acronyms

| | |
|-----------|---|
| E_{res} | = end-systolic fiber elastance |
| τ_L | = time constant of relaxation (zero asymptote method) |
| τ_D | = time constant of relaxation (variable asymptote method) |
| k_c | = chamber stiffness constant |
| k_m | = myocardial stiffness constant |
| LV | = left ventricular |

noninvasive studies have shown impaired filling of the hypertrophied left ventricle in children. However, invasive standards of LV diastolic properties, i.e., time constant of relaxation and myocardial stiffness constant, have rarely been studied in children with congenital pressure overload hypertrophy (12).

Therefore, the present investigation had two principal aims: (1) to evaluate the effect of myocardial hypertrophy on both systolic and diastolic properties of the left ventricle in children, and (2) to evaluate the phenomenon of relaxation in children at controlled heart rates and without the confounding effects of varying heart rates in children of different ages. To answer these questions we studied systolic and diastolic properties of the hypertrophied myocardium of children with congenital aortic stenosis or coarctation of the aorta. Since relaxation is heart rate dependent, we compared LV relaxation between children of different ages at matched heart rates. The relaxation-frequency relationship described in this study provides the first description of this relationship in human beings. We hypothesize that, in children with left ventricular hypertrophy, diastolic dysfunction may precede systolic dysfunction. Moreover, the active relaxation component of diastolic function may be affected earlier than passive filling characteristics of diastole.

Methods

Patient population. We studied two groups of patients: the group with LV hypertrophy constituted the experimental group and the group with normal left ventricles formed the control group. The experimental group (age range 2.5–10.5 years), consisted of 10 children with hypertrophied left ventricles undergoing balloon valvuloplasty/angioplasty: seven with congenital aortic stenosis, two with coarctation of the aorta, and one patient with supraventricular aortic stenosis. The control group (age range 3.0–10.1 years) consisted of nine children undergoing cardiac catheterization: three for electrophysiology studies, three for mild valvar pulmonic stenosis, and three for coil embolization of tiny patent ductus arteriosus without oximetric evidence of left-to-right shunt. The patients in the control group had normal, nonhypertrophied left ventricles based on echocardiograms. The patients with mild pulmonic stenosis had a peak-to-peak gradient of 31 ± 6 mm Hg, low right ventricular end-diastolic pressures (4.8 ± 1.7 mm Hg) and normal right ventricular dimensions. Moreover, there was

no echocardiographic evidence of flattening or compression of the interventricular septum towards the left ventricle. None of the three patients undergoing electrophysiology studies had any evidence of preexcitation. Written informed consents were obtained from parents of all patients, and the experimental protocol was approved by the Institutional Review Board.

Techniques. All studies were performed in the cardiac catheterization laboratory under sedation with oral chloral hydrate followed by parenteral ketamine. High fidelity LV pressure measurements were performed at end expiration by a 2 Fr Millar micromanometric catheter (SPC-320; Millar Instruments, Houston, Texas) introduced through the lumen of the pig-tail catheter. To alter the loading conditions, inferior vena caval occlusion was performed for 8–10 seconds by a 5-Fr. balloon atrial septostomy catheter with an oversized balloon (Baxter Healthcare Corporation, Santa Ana, California). A minimum of eight cardiac cycles were evaluated during the decrease in preload caused by vena caval occlusion. The heart rate was closely monitored during vena caval occlusion and served as an indirect indicator of autonomic stimulation. Caval occlusion was visualized fluoroscopically to ensure a snug fit at the junction of the right atrium and inferior vena cava. Two-dimensional echocardiography was performed to obtain a standard apical four-chamber view of the heart during inferior vena caval occlusion. The two-dimensional images, micromanometric pressure tracings, phonocardiographic recording of heart sounds, and electrocardiograms were recorded simultaneously on video tape. After vena caval occlusion, a bipolar pacing catheter was positioned in the high right atrium, and micromanometric LV pressure tracings and dP/dt were recorded during atrial pacing at heart rates of 110, 120, 130, 140, 150, and 160 per minute.

Measurements and calculations. Left ventricular mass was calculated from M-mode echocardiography and was indexed to height as described previously from our center (13). Left ventricular volume was calculated by two-dimensional echocardiography from the formula for an ellipsoidal model (14): $V = \pi/6 \cdot L \cdot D^2$, where V = left ventricular volume in ml, L = inner major axis in cm, and D = inner minor axis in cm.

The end-diastolic volume and wall thickness were measured at the peak of the R wave of the electrocardiogram. The end-systolic volume, wall thickness, and the end-systolic pressure were measured at end-ejection, i.e., at the first high-frequency component of the second heart sound. End-systolic midwall circumferential wall stress (σ_{es}) was calculated from Mirsky's thick-walled ellipsoid model (15) and expressed as $g \cdot cm^{-2}$: $\sigma_{es} = P \cdot (B/h) [1 - (B^2/2A^2) - (h/2b)]$, where P is the left ventricular end-systolic pressure in mm Hg, h is the end-systolic wall thickness of the left ventricle in cm, A is the midwall semimajor axis ($[L + h]/2$) at end-systole in cm, and B is the midwall semiminor axis ($[D + h]/2$) at end-systole in cm.

End-diastolic circumferential wall stress (σ_{ed}) was calculated by the same formula, where P is the left ventricular end-diastolic pressure in mm Hg, h is the end-diastolic wall thickness of the left ventricle in cm, A is the midwall semimajor

axis ($([L + h]/2)$) at end-diastole in cm, and B is the midwall semiminor axis ($([D + h]/2)$) at end-diastole in cm.

Left ventricular natural strain was calculated as the deformation of the left ventricle at the semiminor axis: $\varepsilon = L_n B/B_0$, where ε is the natural strain, L_n is the natural logarithm, B is the midwall semiminor axis dimension (cm) at end-diastole, and B_0 is the unstressed midwall semiminor axis dimension (cm) at zero stress. However, in the intact human heart, B_0 is difficult to measure directly and requires large extrapolations to measure it indirectly. Therefore, LV strain was computed as $L_n(B/B_{\min})$, where B_{\min} was minimum left ventricular midwall semiminor axis dimension (cm) at the lowest measurable stress calculated at the maximum vena caval occlusion (16,17).

Evaluation of systolic function. Systolic contractile function was assessed from the end-systolic circumferential wall stress (σ_{es})-end-systolic volume (V_{es}) relationship. The slope of the linear regression of the instantaneous stress-volume points produced by vena caval occlusion was referred to as the end-systolic fiber elastance (E_{fes}), to distinguish it from the more commonly used end-systolic chamber elastance (E_{es}) derived from the end-systolic pressure volume relationship (ESPVR) (18). For comparison between patients of different sizes, the E_{fes} was normalized by fitting stress versus normalized volume by a linear regression. The volume was normalized by dividing the left ventricular volume by mass and the result was expressed per 100 g of LV myocardium (19,20). Due to possible nonlinearity of this relation, especially at low levels of stress, linear regression for calculation of E_{fes} was performed only at relatively physiologic ranges of stress. The volume intercept of E_{fes} at the lowest stress ($40 \text{ g}\cdot\text{cm}^{-2}$) achieved by vena caval occlusion was termed V_{40} (21). All measurements of systolic function were performed at the baseline heart rate. Systolic function of the left ventricle was also assessed by the shortening fraction calculated from M-mode echocardiography as follows: shortening fraction(%) = $D_{ed} - D_{es}/D_{ed} \times 100$, where D_{ed} is the end-diastolic dimension in cm and D_{es} is the end-systolic dimension in cm.

Evaluation of diastolic function. Diastolic function has two components: active relaxation and passive diastolic properties. Active relaxation was assessed by calculating the time constant of LV relaxation (τ), whereas passive diastolic properties were assessed by measuring the chamber stiffness constant (k_c) and myocardial stiffness constant (k_m).

Time constant of LV relaxation (τ). Isovolumic relaxation period was defined as the period from peak negative dP/dt to 5 mm Hg above the LV end-diastolic pressure of the following beat. Tau was derived from micromanometric recordings of LV pressure by two techniques: the Weiss method (τ_L), which assumes a monoexponential fall in pressure to a zero asymptote (22), and the Raff and Glantz method (τ_D), which assumes a variable pressure asymptote (23). An average value of τ was calculated at a high sampling rate of 2 ms and from four beats, at end-expiration. All comparisons of time constant of relaxation between patients were performed at a constant heart rate of 120 beats per minute generated by right atrial pacing.

Normalized chamber stiffness constant (k_c). LV chamber stiffness constant was calculated from the diastolic pressure-volume data generated by vena caval occlusion using the exponential curve equation (Delta Graph, Deltapoint Inc., Monterey, California): $P = A \cdot e^{kV}$, where P is the LV end-diastolic pressure, e is the base of the natural logarithm, A is the y intercept, k is the chamber stiffness constant, and V is LV end-diastolic volume.

To allow for interpatient comparison, k was normalized using the concept of volume elasticity proposed by Mirsky (24). Therefore, the normalized chamber stiffness constant (k_c) was calculated as the slope of the linear regression between $V(dP/dV)$ versus P , where $dP/dV = kP$.

Myocardial stiffness constant (k_m). LV myocardial stiffness constant (k_m) was calculated from the diastolic stress-strain relationship generated by vena caval occlusion using a simple elastic model: $\sigma_{ed} = A \cdot e^{k_m \varepsilon}$, where σ_{ed} is the LV end-diastolic stress, e is the base of the natural logarithm, A is the y intercept, k_m is a simple elastic constant of myocardial stiffness, and ε is the LV natural strain.

Force-frequency and relaxation-frequency relationships.

To determine the combined effects of hypertrophy and heart rate on systolic and diastolic properties in children with aortic stenosis or coarctation, we examined the response of isovolumic contraction and relaxation to incremental atrial pacing. Therefore, the force-frequency relationship was derived by plotting left ventricular dP/dt_{\max} versus heart rate, and the relaxation-frequency relationship was derived by plotting τ versus heart rate. The slopes of the force-frequency and relaxation-frequency relationships calculated from patients with LV hypertrophy were compared with those from control patients.

Statistics. Data were expressed as mean \pm SD unless otherwise stated. Patients with LV hypertrophy and those with normal left ventricles were compared by the unpaired t -test, and a p value of <0.05 was considered to be significant. Analysis of variance was performed for multiple paired observations followed by a Bonferroni t -test.

Results

Clinical and hemodynamic data. The clinical and hemodynamic data are presented in Table 1. The mean peak-to-peak pressure gradient across the site of aortic stenosis or coarctation was 49.2 ± 5.3 mm Hg. The normalized LV mass was significantly increased and the LV end-systolic wall stress was lower in patients with LV hypertrophy (Table 1). The LV end-diastolic pressure was elevated in the patients with LV hypertrophy (14.7 ± 2.4 vs. 10.3 ± 2.2 mm Hg, $p < 0.05$) but the LV end-diastolic wall stress was not significantly different between the two groups (28.3 ± 11.4 vs. $35.1 \pm 8.2 \text{ g}\cdot\text{cm}^{-2}$, $p > 0.05$). The heart rate remained constant during the brief caval occlusion employed to generate E_{fes} .

LV systolic function. In all patients in the experimental group, shortening fraction was significantly higher than in the control group ($45 \pm 6\%$ vs. $33 \pm 7\%$, $p < 0.05$). During vena caval occlusion end-systolic wall stress decreased by an average

Table 1. Clinical and Hemodynamic Variables

| Variables | Control Group (n = 9) | Hypertrophy Group (n = 10) |
|---|-----------------------|----------------------------|
| Age (yrs) | 5.7 ± 2.5 | 6.3 ± 2.8 |
| Heart Rate (beats per minute) | 95.2 ± 8.1 | 88.3 ± 6.3 |
| Peak-to-peak Gradient (mm Hg) | — | 49.2 ± 5.3 |
| Normalized LV mass (g·m ⁻¹) | 43.6 ± 15.1 | 81.9 ± 16.4* |
| LVEDP (mm Hg) | 10.3 ± 2.2 | 14.7 ± 2.4† |
| h _{cd} (cm) | 0.53 ± 0.17 | 0.83 ± 0.16† |
| σ _{es} (g·cm ⁻²) | 136.4 ± 28.3 | 81.3 ± 23.9* |
| σ _{cd} (g·cm ⁻²) | 35.1 ± 8.2 | 28.3 ± 11.4 |
| E _{f_{es}} (g·cm ⁻² ·mL ⁻¹ ·100 g) | 6.9 ± 1.3 | 7.3 ± 1.2 |
| V ₄₀ (ml) | 4.1 ± 3.2 | 5.0 ± 3.1 |
| dP/dt _{max} (at 110 bpm) (mm Hg·s ⁻¹) | 1748.6 ± 378.4 | 1842.6 ± 315.4 |
| dP/dt _{max} (at 150 bpm) (mm Hg·s ⁻¹) | 2368.3 ± 447.6 | 2452.6 ± 231.4 |
| τ _L (at 120 bpm) (ms) | 21.8 ± 2.2 | 27.3 ± 2.3* |
| τ _D (at 120 bpm) (ms) | 34.3 ± 3.3 | 43.2 ± 3.1* |
| k _c | 2.5 ± 0.3 | 2.9 ± 0.4 |
| k _m | 6.1 ± 1.5 | 6.6 ± 1.6 |

*p < 0.001, †p < 0.05. LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; h_{cd} = LV posterior wall thickness at end-diastole; σ_{es} = end-systolic circumferential wall stress; σ_{cd} = end-diastolic circumferential wall stress; E_{f_{es}} = end-systolic fiber elastance; V₄₀ = volume intercept at stress of 40 g·cm⁻²; τ_L = time constant of relaxation (zero asymptote method); τ_D = time constant of relaxation (variable asymptote method); k_c = LV chamber stiffness constant; k_m = myocardial stiffness constant.

of 32 ± 9%, and end-systolic volume decreased by an average of 42 ± 11%. End-systolic stress-volume data were well fitted by a linear regression (mean value of r = 0.978 ± 0.007 in control group and 0.982 ± 0.003 in experimental group). LV systolic function assessed by end-systolic fiber elastance (E_{f_{es}}) was not significantly different in patients with left ventricular hypertrophy versus controls (7.3 ± 1.2 vs. 6.9 ± 1.3 g·cm⁻²·mL⁻¹·100 g, p > 0.05).

LV diastolic function. LV relaxation was slower in patients with LV hypertrophy, evidenced by prolongation of the time constant of relaxation (τ) measured at a constant heart rate of 120 per minute (τ_L: 27.3 ± 2.3 vs. 21.8 ± 2.2 ms, p < 0.001; and τ_D: 43.2 ± 3.1 vs. 34.3 ± 3.3 ms, p < 0.001) (Fig. 1).

Normalized chamber stiffness constant (k_c) remained un-

Figure 1. Time constant of relaxation measured at a constant heart rate of 120 beats per minute, by the zero asymptote method (τ_L), was prolonged in children with myocardial hypertrophy suggesting slower relaxation. Error bars represent standard deviation (*p < 0.001).

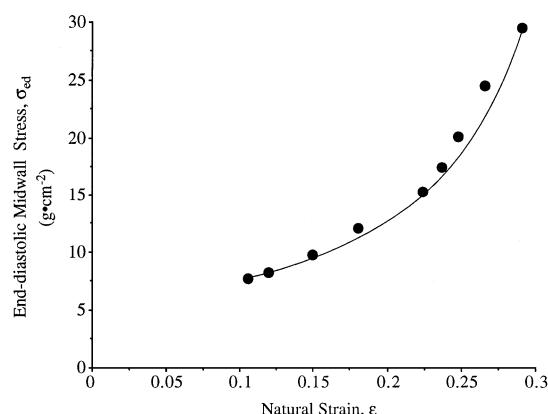
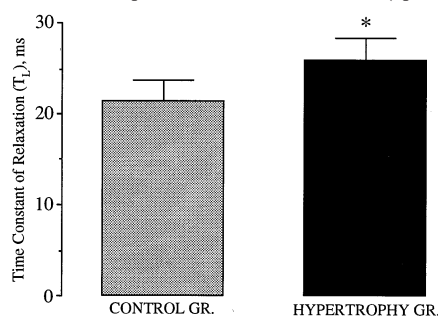


Figure 2. Left-ventricular end-diastolic stress-strain relationship in a patient with myocardial hypertrophy, depicting a typical exponential curve fit (R² = 0.99).

changed in patients with LV hypertrophy (2.9 ± 0.4 vs. 2.5 ± 0.3, p > 0.05).

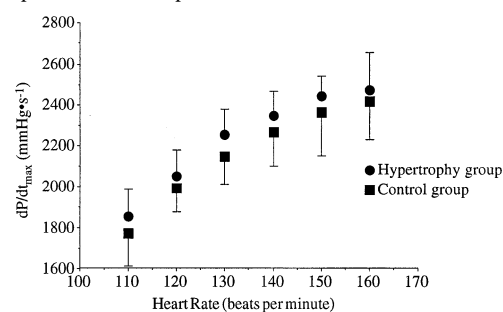
Myocardial stiffness constant (k_m) also remained unchanged in the presence of LV hypertrophy (6.6 ± 1.6 vs. 6.1 ± 1.5, p > 0.05).

Both the end-diastolic pressure-volume data and stress-strain data from all patients (control and experimental) fitted well to an exponential curve (Fig. 2) with high correlation coefficients (mean r = 0.985 ± 0.003 for pressure-volume data, and mean r = 0.987 ± 0.008 for stress-strain data).

Force-frequency and relaxation-frequency relationships.

The force-frequency (dP/dt_{max} vs. heart rate) relationship showed a stepwise increase in dP/dt_{max} with increasing heart rate. An increase in heart rate from 110 to 150 per minute increased the dP/dt_{max} by 33% in the experimental group and 35% in the control group of patients (Fig. 3). In contrast, LV end-diastolic pressure dropped by 33% in the experimental group and by 38% in the control group when heart rate increased from 110 to 150 per minute. Although dP/dt_{max} increased monotonically up to a heart rate of 160 per minute in

Figure 3. The force-frequency relationship (dP/dt_{max} vs. heart rate) is depicted in the control (squares) and hypertrophy (circles) groups. The dP/dt_{max} increases with each increment in heart rate, producing a positive force-frequency relationship in each group. At each level of heart rate the mean dP/dt_{max} is not significantly different and the slope of the force-frequency relationship remains unchanged between the two groups. Error bars represent standard error of mean.



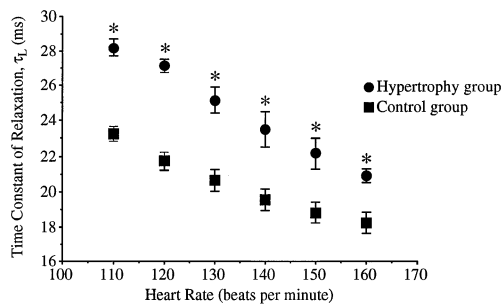


Figure 4. The relaxation-frequency relationship (τ vs. heart rate) is depicted in the control (squares) and hypertrophy (circles) groups. τ shortens with increasing heart rate suggesting improved relaxation, however, the slope of the relaxation-frequency relationship remains unaltered between the control and hypertrophy groups. Error bars represent standard error of mean (* $p < 0.05$).

virtually all patients, the dP/dt_{\max} decreased abruptly at a heart rate of 160 per minute in one patient in the LV hypertrophy group and in two patients in the control group.

The relaxation-frequency relationship (τ vs. heart rate), likewise, showed a gradual decrease in τ with increasing heart rate. However, one patient in the control group showed abrupt prolongation of τ at a heart rate of 160 per minute. This same patient had also shown a decrease in dP/dt_{\max} at the same heart rate. In the experimental group, the mean dP/dt_{\max} at each heart rate increment was not significantly different from the measurements of mean dP/dt_{\max} made in the control group (Fig. 3). In contrast, mean τ was significantly prolonged at each level of heart rate, and the relaxation-frequency relationship was shifted upwards (Fig. 4), suggesting prolonged relaxation at each level of heart rate. Importantly, the slopes of the force-frequency and relaxation-frequency relationships remained unaffected by LV hypertrophy (slope of force-frequency relationship: 16.6 ± 3.2 vs. 15.6 ± 3.8 mm Hg·s⁻¹·min⁻¹, $p > 0.05$; slope of relaxation-frequency relationship: τ_L method, -0.116 ± 0.027 vs. -0.096 ± 0.025 , ms·min⁻¹, $p > 0.05$; and τ_D method, -0.123 ± 0.030 vs. -0.130 ± 0.035 , ms·min⁻¹, $p > 0.05$).

Discussion

In this study we found that in the hypertrophied myocardium of children exposed to pressure overload, systolic function remains unchanged and passive diastolic properties measured by the chamber stiffness and myocardial stiffness are not increased. At matched heart rates, relaxation is prolonged in the hypertrophied myocardium of conscious, sedated children. Incremental increases in heart rate produced improvement in both contraction and relaxation, and the combined effect of hypertrophy and heart rate does not influence the force-frequency and relaxation-frequency relationships.

Effect on systolic properties. In children with pressure overload hypertrophy, most studies have shown supernormal ejection performance (8,25), which was corroborated by our study. This does not necessarily indicate an increase in con-

tractility but rather may reflect a decrease in wall stress (26). In our study, systolic performance assessed by a relatively load-independent index, $E_{r_{es}}$, remained unaffected by myocardial hypertrophy in children. The findings of our study are consistent with the findings of increased shortening indices but unchanged end-systolic stress-strain relationship in immature sheep (27) and mature dogs (28) with pressure overload hypertrophy.

The slope of the end-systolic pressure volume relationship (ESPVR) is referred to as end-systolic chamber elastance (E_{es}) (29). However, the ESPVR is dependent on chamber size and wall thickness, which disallows meaningful comparison of systolic function between ventricles of different sizes and between normal and hypertrophied ventricles. In the hypertrophied ventricle it has been proposed that the slope of the end-systolic stress-volume relationship, i.e., fiber elastance, is a more accurate index of contractility than the slope of the ESPVR, i.e., chamber elastance (18). In order to compare fiber elastance between hearts of different sizes, we normalized LV volume by dividing it by LV mass, as suggested by Sagawa and others (19,20). In children with myocardial hypertrophy due to congenital aortic stenosis the reduction in systolic wall stress seen in this study is quite characteristic (8,26). This is in contrast to acquired aortic stenosis of adults in whom the systolic wall stress either normalizes if the myocardial hypertrophy is adequate or increases if the hypertrophy is inadequate.

Effect on diastolic properties. Diastolic function has been divided into two components: active relaxation and passive diastolic properties. The active relaxation component was impaired in children with myocardial hypertrophy reflected by prolongation of τ at matched heart rates. Prior evaluation of τ in children has been limited to a single study in older children (mean age 14.8 ± 4.3 years), who had undergone repair of coarctation of aorta 3–12 years prior to the study (30). Due to difficulty in recruiting normal children, this experimental group was compared with a control group consisting of normal adults (mean age 40.0 ± 13.0 years) and the heart rates were not strictly matched by pacing. In our study, comparison of τ between experimental and control groups was made at a strictly controlled heart rate of 120 per minute. This heart rate of 120 per minute may be closer to the natural heart rates of some children, whereas it may be less close in others. However, since τ is quite sensitive to heart rate we chose to compare τ at a matched heart rate that was common for all children.

Studies on chamber and myocardial stiffness constants have yielded conflicting results in adults with pressure overload hypertrophy (31–35). These studies have suggested an increase in stiffness versus no change. Studies in children are limited and have measured single-beat myocardial stiffness from several points during the diastolic cycle of a single beat (12). This may not allow matching of stress, as the levels of stress may vary between patients when a single beat is compared. The measurement of stiffness over a wider range of stresses generated by altering the loading conditions, performed in our study, allows comparison of myocardial stiffness at common levels of

stress. In adults, the value of k_m is not influenced by LV muscle mass but is increased in the presence of significant interstitial fibrosis (36). In children, there is a concern that in pressure overload hypertrophy due to congenital aortic stenosis or coarctation, if the stress is not relieved it may lead to myocardial fibrosis (37). A relatively normal value of k_m suggests that in children with myocardial hypertrophy produced by moderate obstruction, an increase in fibrous tissue is unusual despite being exposed to chronic pressure overload. In children the effect of more severe obstruction on myocardial stiffness is unknown, and may be difficult to study, as virtually all interventions aimed at reducing the obstruction to the left ventricle in children are undertaken at moderate degrees of obstruction.

Force-frequency relationship. The force-frequency relationship has been used extensively in isolated muscle preparations (Bowditch staircase or *treppe* effect) (38). More recent *in vivo* experiments on primates have shown that the force-frequency relationship is biphasic in nature, consisting of a positive phase and a negative phase separated by a “critical heart rate.” Therefore, the response of isovolumic contraction (dP/dt_{max}) to incremental pacing was positive only up to the critical heart rate, after which dP/dt_{max} started to decline (39). Due to a potential for inducing arrhythmias in children and due to restrictions imposed by the Institutional Review Board, in our study incremental pacing was stopped at a heart rate of 160 per minute. Therefore, for most patients a critical heart rate was not achieved. However, in one patient with myocardial hypertrophy and in two control patients, dP/dt_{max} decreased abruptly at a heart rate of 160 per minute, suggesting a critical heart rate had been reached. Due to inherent limitations in studying humans, in this study we evaluated only the positive limb of the force-frequency relationship, which provided useful information on the combined role of hypertrophy and heart rate on contractile function. Heart rate plays an important role in myocardial performance, however, experimental results of chronotropic effects on contractility are conflicting. Some studies on conscious animals suggest minimal chronotropic effects on contractility (40), while others propose a significant positive effect of heart rate on contractility (39,41). In our study on conscious, sedated children an increase in heart rate from 110 to 150 beats per minute increased dP/dt_{max} by 33% in the hypertrophy group and by 35% in the control group. The slope of the positive limb of the force-frequency relationship remained unchanged, suggesting that myocardial hypertrophy has no significant effect on heart rate–related increase in contractility. Due to its preload dependence, dP/dt_{max} was not compared between the experimental and control groups at each level of heart rate, but rather the slope of dP/dt_{max} versus heart rate was compared. The slope of the force-frequency relationship has been used to assess contractility during dobutamine infusion before and after induction of pacing induced heart failure in pigs (42).

Relaxation-frequency relationship. Similar to the force-frequency relationship, the relaxation-frequency relationship is often described as biphasic in nature, characterized by an initial descending limb, suggesting improved relaxation fol-

lowed by an ascending limb suggesting impaired relaxation. The heart rate at which this transition occurs is also called the critical heart rate (39). In our study, relaxation also improved with increments in heart rate in both hypertrophy and control group of patients. However, in the patients with myocardial hypertrophy, relaxation was prolonged when compared with the control patients at matched heart rates. Nevertheless, the slope of the descending limb of the relaxation-frequency relationship remained similar to that of the control group. In severe LV hypertrophy induced in rats by abdominal aortic banding, Ca^{2+} uptake function of the sarcoplasmic reticulum (SR) decreased and the message and protein levels of SR Ca^{2+} pump decreased concomitantly (43). However, impaired Ca^{2+} uptake by the SR may be one of the several mechanisms that may be responsible for prolongation of relaxation. Other mechanisms of myocardial relaxation include: 1) inactivation (energy-dependent unbinding of Ca^{2+} from troponin C leading to detachment of actin-myosin cross-bridges), 2) excessive changes in load, and 3) nonuniformity of load and inactivation in time and space (44). Geometric changes in myocyte alignment may also play a role. The effect of load on relaxation, however, is controversial. Some investigators have shown that in conscious dogs, LV relaxation is dependent on afterload (45), whereas others have shown that in the intact canine heart, afterload-dependent slowing of relaxation could not be attributed to an increased total load, but rather to the altered loading sequence associated with an increase in afterload (46). Other investigators evaluating the afterload-dependence of relaxation in humans have found that alteration in afterload does not affect relaxation when heart rate is maintained constant (47). Therefore, the prolonged relaxation noted in our study may result from myocardial hypertrophy. Alternatively, increased afterload or altered loading sequence may play a role in prolonging relaxation in these children with myocardial hypertrophy. Prolonged relaxation may even be a compensatory adaptation to pressure-overload hypertrophy.

Limitations of the study. One of the important limitations of our study is recruitment of patients with completely “normal” left ventricles for the control group of patients. Due to superior noninvasive imaging modalities, virtually no patient with completely normal hearts undergoes diagnostic catheterization. Difficulty of recruiting children with completely normal hearts has also been experienced by previous investigators assessing time constant of relaxation in children, who used adult patients as controls (30). In our series all patients in the control group were children; however, we included three patients with mild pulmonic stenosis as controls. This raises the issue of interaction between right and left ventricles. Therefore, in an effort to minimize this interaction between right and left ventricles, we included patients with only mild pulmonic stenosis, who had normal right ventricular dimensions, low right ventricular end-diastolic pressures, and who manifested no significant compression of the interventricular septum on two-dimensional or M-mode echocardiography.

In this study elastance and myocardial stiffness constants showed a slight tendency to increase in the patients with

myocardial hypertrophy but the difference did not achieve statistical significance. The lack of difference in these indices could be a reflection of inadequate sensitivity of these indices or a reflection of the modest number of patients, which is an important limitation of this study.

In our study on children, autonomic blockade was not employed and heart rate was used as an indirect indicator of autonomic influences. We generated rapid decrease in preload by brief (8–10-secs) vena caval occlusion, which does not significantly stimulate autonomic reflexes (48,49). To assess the role of autonomic reflexes resulting from pacing, Freeman et al studied dogs after pharmacologic blockade of the autonomic nervous system using atropine and propranolol. The increase in dp/dt_{\max} and the decrease in τ in response to increased pacing was very similar in autonomically intact dogs and in those studied after autonomic blockade (50).

It has been shown that dp/dt_{\max} is dependent on preload, and an increase in dp/dt_{\max} may not necessarily indicate an increase in contractility, but may reflect an increase in preload. In our study during assessment of dp/dt_{\max} , simultaneous preload, i.e., LV volume or dimension, was not measured. Nevertheless, during increasing heart rates the LV end-diastolic pressure decreased monotonically, suggesting a corresponding decrease in preload. Such decrease in preload with incremental pacing has also been described in conscious animals in whom preload was assessed from LV end-diastolic volume rather than from end-diastolic pressure (39). Therefore, the increase in dp/dt_{\max} noted during incremental pacing in children occurred in the face of decreasing preload and represents a true increase in contractility. However, the total magnitude of the force-frequency relationship may have been underestimated by not correcting dp/dt_{\max} for preload. The preload dependence is a limitation of the force-frequency relationship in the in vivo experiment versus in isolated muscle preparations, where preload is held constant.

In this study myocardial stiffness was calculated from the simple elastic relationship rather than the more complex viscoelastic relationship. The viscoelastic model that includes a parallel viscous element represents elastic properties more accurately. In the viscoelastic model stress depends not only on strain but also on strain rate, whereas in the simple elastic model the strain rate is not incorporated. However, the parallel viscous influences are important during rapid filling, i.e., at early- and possibly mid-diastole, but are minimal in late-diastole (51). Moreover, during late-diastole strain rate is low (51) and may be ignored. Therefore, although the viscoelastic model may be superior during early- and mid-diastole, during end-diastole the simple elastic model may provide a relatively accurate estimate of stiffness. In our study myocardial stiffness was calculated at end-diastole when viscous influences are minimal.

Conclusions. Our results indicate that in conscious, sedated children with myocardial hypertrophy due to congenital aortic stenosis or coarctation of aorta, systolic function measured by an index of force generation remained unchanged. LV relaxation evaluated at matched heart rates was impaired, but

passive diastolic property of the left ventricle remains unaffected. Especially, a normal myocardial stiffness constant suggests absence of significant fibrosis in pressure-overloaded, hypertrophied myocardium of children. Incremental increases in heart rate produced incremental improvement in both contraction and relaxation. The combined effect of hypertrophy and heart rate does not alter the force-frequency and relaxation-frequency relationships, which are preserved in children with myocardial hypertrophy. We speculate that a reduction in wall stress characteristically seen in these children helps maintain normal cardiac function in the hypertrophied left ventricle of children. Our results imply that abnormality of relaxation may precede abnormalities of passive diastolic properties of the left ventricle in children.

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